CRITICAL REVIEW IN PHARMACEUTICAL SCIENCES

ISSN 2319-1082

Review Article

RECENT TRENDS IN SCOPE AND OPPORTUNITIES OF CONTROL RELEASE ORAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines. Their physical, chemical, and biopharmaceutical attributes distinct from small molecule drugs demand novel controlled release technologies to diminish barriers for oral delivery, such as instability in GI tract and poor absorption. Those unmet technology needs create great opportunities for research, development, and innovation. It isoptimistic that breakthroughs in controlled oral delivery for water-insoluble drugs and biopharmaceuticals will have a significant impact on pharmaceutical and biotechnology industry. Significant advances have been made in drug delivery technologies throughout the past 3 decades, and drug delivery at a desired release rate is now possible. Even highly sophisticated drug delivery technologies, however, often fail to produce marketable oral controlled-release dosage forms, as a result of the physiological limitations of the gastrointestinal (GI) tract and/or the utilization of non-feasible pharmaceutical components. In oral drug delivery, there are many scientific challenges that could be studied for years to come, and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level. This article examines several aspects in oral drug delivery requiring implementation of novel ideas to improve oral drug delivery systems. Drug Delivery is a burgeoning field that represents one of the major research and development focus areas of pharmaceutical industry today, with new drug delivery system sales exceeding 10 billion dollars per year.

KEYWORDS : oral drug delivery system, proteins, gastrointestinal

ISSN 2319-1082

INTRODUCTION

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid, dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. To design the oral controlled release tablet to increase the residence time of the drug in to the stomach and release for extended period of time in order to; Increase bioavailability of the drug, Reduce the dosing frequency, Improve patient compliance. Interest in controlled and sustained release drug delivery has increased considerably during the past decade and, in selected areas, it's now possible to employ fairly sophisticated system which is capable of excellent drug release control. The self-regulating insulin delivery system by using lectin and oral osmotic tablet are illustrative examples. However, for oral administration, all of these systems are limited to some extent because of gastrointestinal (GI) transit. Thus, the duration of most oral sustained release products is approximately 8-12 hours due to the relatively short GI transit time, and the possibilities to localize drug delivery system in selected regions of the gastrointestinal tract (GIT) for the purpose of localized drug delivery are under investigation. The controlled drug delivery system is one, which delivers the drug at a predetermined rate, locally or systemically for a predetermined period of time. The targeted drug delivery system is one, which delivers the drug only to its site of action and not to the nontarget organs or tissues. The two main advantages of controlled drug delivery systems are: maintenance of therapeutically optimum drug concentrations in the plasma through zero-order release without significant fluctuations; and elimination of the need for frequent single dose administrations

SCOPE AND OPPORTUNITIES

The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract.

ISSN 2319-1082

Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains the most desirable. For obvious reason, water soluble drugs are more difficult to deliver orally in sustained or controlled release manner than lipophilic drugs. Attempts have been made to regulate the release process by incorporating hydrophobic fillers within the system or by coating the drug with poorly soluble, swollen or non-swollen polymers or other substances. Others used the so called 'hydrodynamically balanced systems' which float in the gastric fluid at the stomach thereby increase the residence time for the device in the GI tract. A new approach has been the use of mucoadhesive systems to increase the residence time of the device within the GI tract. This review focuses on the progress made in the design of controlled/sustained release delivery systems for some water soluble drugs. Highly/freely water soluble diltiazem, captopril and morphine salts have been selected as model drugs due to the leading role they play in their respective field of therapy and their widespread use in treating chronic patients. Particular emphasis is given to delivery systems designed to achieve their once a day dose treatment. Significant advances have been attained in developing and commercializing oral controlled release products. Many platforms are available for delivering small molecule drugs with good aqueous solubility in prolonged or delayed release forms.However, there are significant challenges in developing controlled release formulations for drugs with poor aqueous solubility, which require both solubilization and engineering of release profile. To deliver drugs at zero-order release rate, preferably independent of the gastrointestinal (GI) tract environment, many efforts and achievements have been made besides osmotic pump drug delivery systems.Moreover, many of the new therapeutics under development are large molecules like peptides, proteins, oligonucleotides, and vaccines. Their physical, chemical, and biopharmaceutical attributes, distinct from small molecule drugs, demand novel controlled-release technologies to diminish barriers for oral delivery like instability in the GI tract and poor absorption. Those unmet technology needs create great opportunities for research, development, and innovation. Breakthroughs in controlled oral delivery for water-insoluble drugs and biopharmaceuticals are likely to have a significant impact on the pharmaceutical and biotechnology industries.On the other hand, the continuous improvement of current delivery technologies is also important when it comes to decreasing cost and increasing efficiency. Those advancements include novel excipients, processes, and equipment as new tools formulation scientists can use to develop oral controlled-release formulations.

Oral Drug Delivery Market – Controlled And Sustained Release To Be Major Revenue Generators Oral Drug Delivery Market

GBI Research's report, "Oral Drug Delivery Market – Controlled and Sustained Release to be Major Revenue Generators", provides the key data and analyzes the major challenges and drivers for the Oral Drug Delivery Market. The report also provides in-depth analysis of unmet needs, drivers and barriers that impact the global Oral Drug Delivery Market.

ISSN 2319-1082

Further, the report provides competitive benchmarking for the leading companies and analyzes the mergers, acquisitions and licensing agreements that shape the global markets. The report is based on proprietary databases, primary and secondary research and in-house analysis by GBI Research's team of industry experts to provide a comprehensive view of the Oral Drug Delivery Market.

Scope

The scope of this report includes:

1. Opportunities and challenges for Oral Drug Delivery Market in the pharmaceuticals industry
2. Market revenues and forecasts for Oral Drug Delivery Market in the global pharmaceutical industry from 2009 to 2016.
3. The key geographies including the US, Europe, Japan and Emerging Hotspots such as India, Singapore and China.
4. Technology trends in Oral Drug Delivery Market. that shape the industry
5. Qualitative analysis of the market drivers, barriers, future outlook and challenges for the Oral Drug Delivery Market.
6. Analysis of competitive landscape and the leading market players.

Reasons to buy

The report will enhance your decision making capability. It will allow you to:

1. Formulate strategies to increase your company's growth by understanding the new growth opportunities in Oral Drug Delivery Market.
2. Differentiate yourself from competitors and develop new solutions for Oral Drug Delivery Market by understanding the current competitive landscape and how it is evolving to meet the increasing demands
3. Draft efficient strategies by understanding best practices, identifying key winners and losers and who is best positioned to take advantage of the emerging market opportunities.
4. Make more informed business decisions from the insightful and in-depth analysis of the market for biomanufacturing by analyzing the key technology trends that shape the growth of this market

CHALLENGES OF ORAL CONTROL DRUG DELIVERY SYSTEMS

Oral solid dosage forms was the preferred route of many drugs. Today, the oral dosage form is still the old and new controlled release products the most widely used forms. After years of development, oral controlled release drug delivery system technology are formed as two major categories:Delayed drug delivery system. Through the use of drugs can block the release of the polymer material forming the core matrix tablets, or tablets containing the drug (pill) core for controlled release coated film to achieve.Delayed drug delivery system. Generally achieved by enteric coating. Controlled release tablets and multi-particle systems (such as the drug pellets, granules, mini tablets and drug crystal, etc.) research, development and production technology

ISSN 2319-1082

is relatively mature. Past two decades, oral controlled release technology has moved from development to production for the center to the center of clinical efficacy, not only for already marketed drugs, more research and development for new drugs monomer. Make sustained and controlled release system has more advantages, including reducing delivery times to improve patient compliance, and better improve the clinical efficacy to reduce the side effects and increase bioavailability. Controlled release formulation of molding technology also takes into account the biological, physical chemistry and mechanics of content, such rational agents designed to reduce the drug in the body, "burst release" of the danger.Pharmacology and clinical aspects in addition to the advantages of controlled release pharmaceutical formulations can also bring economic benefits, it can be intellectual property, brand differentiation and promotion to achieve, in addition to the transfer of technology to other companies may also bring big business profits.Although there are many reports of controlled release technology, but commercial applications are few reasons, mainly for drug release from polymer materials block the price too high, or too much production requirements professional. Thus the most successful oral controlled release system should have the following characteristics, namely, the use of polymer materials widely available, and can achieve large-scale production.USP on controlled release system is defined as: "to change the drug release time, process and / or location to achieve the purpose of the use of more convenient and traditional agents can not achieve the therapeutic effect." This sentence can be seen through the out sustained and controlled release also includes changes in the location of drug release. Successful design of controlled release formulations need to fully understand the mechanism of drug release; drug size, shape, structure-activity relationship of molecular structure until all have a significant impact on drug release. Compared with the traditional tablet, multi-particle drug delivery systems less affected by food, so is the product of choice for sustained and controlled release dosage forms [1]. Ideal controlled release preparation of multi-particle system is film coating, and coating systems for controlled release, film can be of good permeability.

The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for a duration required for optimal treatment.
- Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either

ISSN 2319-1082

bypass or minimize the extent of hepatic metabolic effect.

Controlled Drug Delivery Systems

The oral and other therapeutic systems in human use have validated the concept that controlled continuous drug release can minimize the daily dose of a drug required to maintain the required therapeutic effect, while minimizing unwanted pharmacological effects. By minimizing patient intervention, a design feature of therapeutic systems, compliance is automatically enhanced. Oral drug delivery systems, in particular, have required innovation in materials science to provide materials biocompatible during prolonged contact with body tissues, bioengineering to develop drug delivery modules, and clinical pharmacology for elucidation of drug action under conditions of continuous controlled drug administration. Recent work in advanced oral delivery has been primarily focused on liposome technology and the concept that substances that are normally destroyed by the stomach can be protected long enough before they could be absorbed downstream. For cost and patient convenience, oral delivery certainly would be an attractive method. The nature of biologic substances, however, with their unique technical problems, will probably limit greatly those that can be delivered orally. Besides, where delivery rate control is critical, oral delivery, even when possible, would probably be insufficiently precise. Oral delivery would also limit the substance to bloodstream delivery to the disease site. Even so, oral controlled drug delivery systems will likely find primary usefulness in specific carefully controlled therapies and prophylactic situations with due regard for drug interactions. This system represents a potentially very significant therapeutic modality. These delivery systems will find usefulness primarily in certain well-defined and well-controllable areas with due regard for individual patient variations. The purpose of the present article is to review oral controlled-release drug delivery systems, with particular emphasis on the practical aspects of testing and fabricating these systems and the underlying mechanisms by which control over drug release rate is accomplished

Conventional oral controlled dosage forms suffer from mainly two adversities[10]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. These problems can be overwhelmed by altering the gastric emptying. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time. Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.[11,12]

- that are locally active in stomach,
- that have an absorption window in the stomach or in the upper small intestine,
- that are unstable in the intestinal or colonic environment,
- have low solubility at high pH values.

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for

ISSN 2319-1082

systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[1]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:[2,3]

- Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance .
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[4]

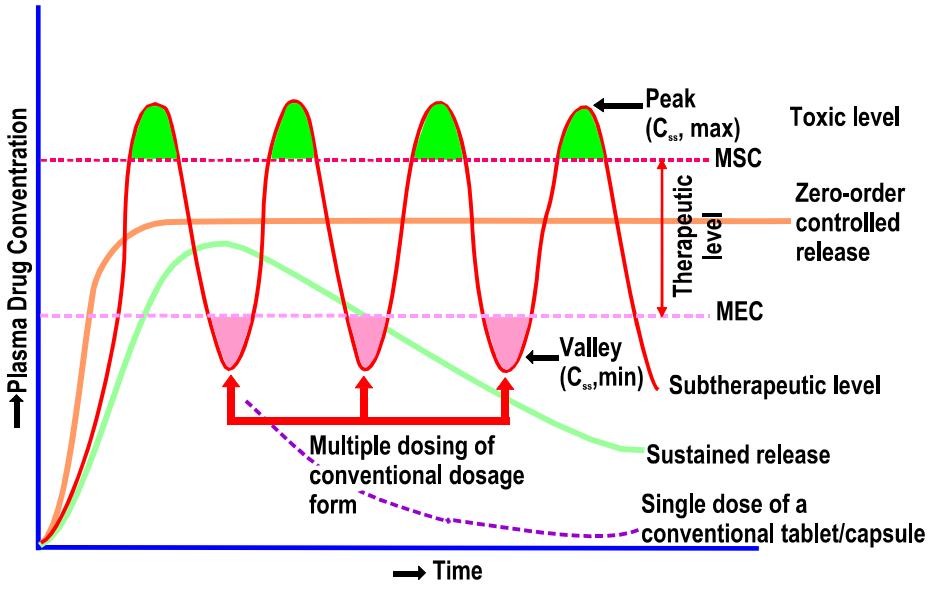

Fig. No. 1- A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

ISSN 2319-1082

Controlled Drug Delivery Systems classification

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[5]

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

More precisely, controlled delivery can be defined as[6]:-

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.
5) A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery System:

1. Avoid patient compliance problems.
2. Employ less total drug
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use.
   d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
   a) Cures or controls condition more promptly.
   b) Improves control of condition i.e., reduced fluctuation in drug level.
   c) Improves bioavailability of some drugs.
   d) Make use of special effects, E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

ISSN 2319-1082

Disadvantages[7]:

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

Gastroretentive Dosage Form (GRDF):

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS).[13]

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.[14]

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as[15] –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
3) GRDFs can be used as carriers for drugs with so-called absorption windows. These

ISSN 2319-1082

substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.

APPROACHES TO GASTRIC RETENTION[20]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

a) Floating Systems:

Floating Drug Delivery Systems (FDDS)[21] have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

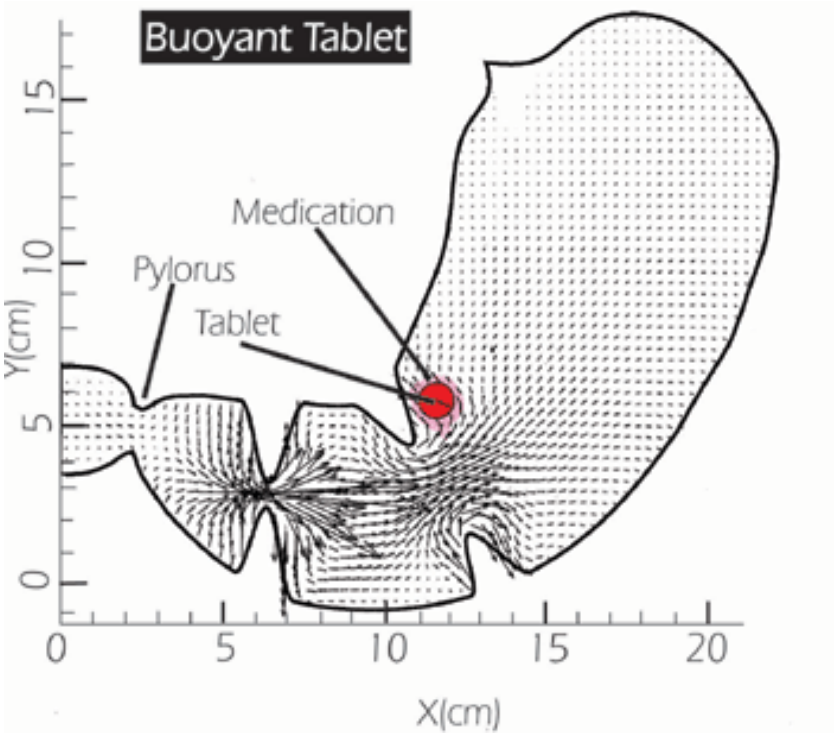

Fig. 2: Graphic of Buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

ISSN 2319-1082

b) Bio/Muco-adhesive Systems:[22]

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin/epithelial surface can be divided into three broad categories :–

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems:[23]

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "*plug type system*", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

d) High Density Systems:-[24]

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 4.

ISSN 2319-1082

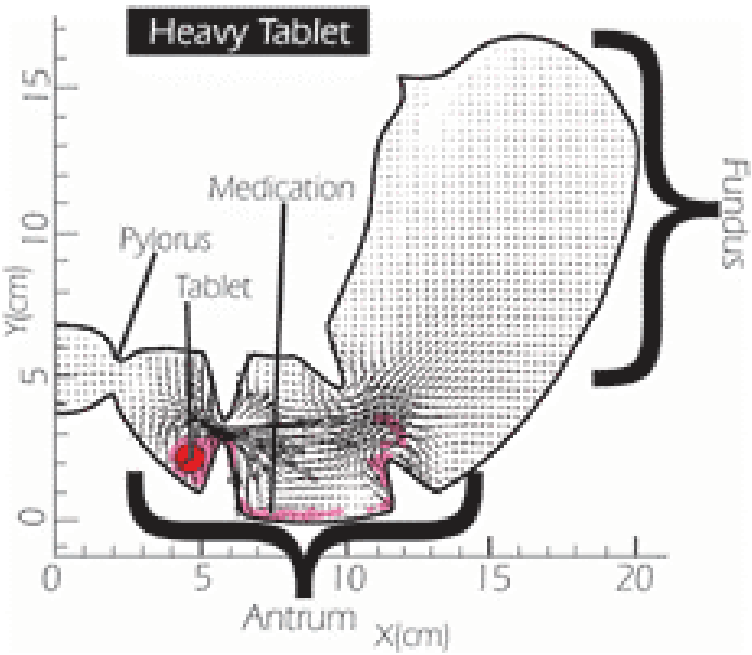

Fig. 3: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum.

e) Incorporation of Passage Delaying Food Agents:-[25]

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

f) Ion Exchange Resins:[26]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems:[10]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists

ISSN 2319-1082

of two components drug reservoir compartment and osmotically active compartment.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)[27,28]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are :

A. Effervescent System, and
B. Non- Effervescent System.

A. EFFERVESCENT SYSTEM:-

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced Sysem (HBS):

These are as shown in Fig.5 and formulated by intimately mixing the CO_2 generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

i. Immediate release layer and
ii. Sustained release layer.

3. Multiple Unit type floating pills:

These system consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

II. Volatile Liquid / Vacuum Containing Systems:

1.Intragastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacum or filled with air or a harmless gas, while drug reservoir is

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encapsulated inside a microprous compartment, as shown in Fig.8.

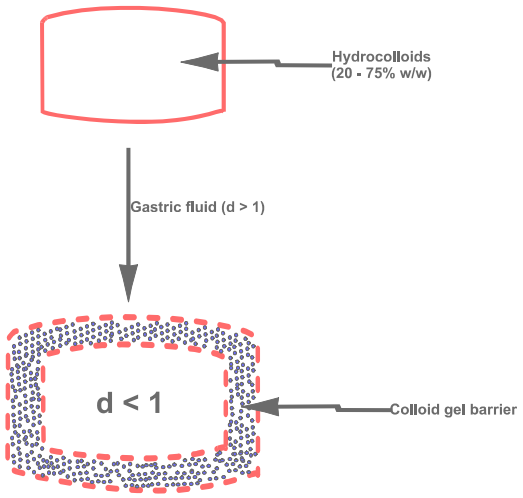

Fig. 4: Intra Gastric Single Layer Floating Tablet.

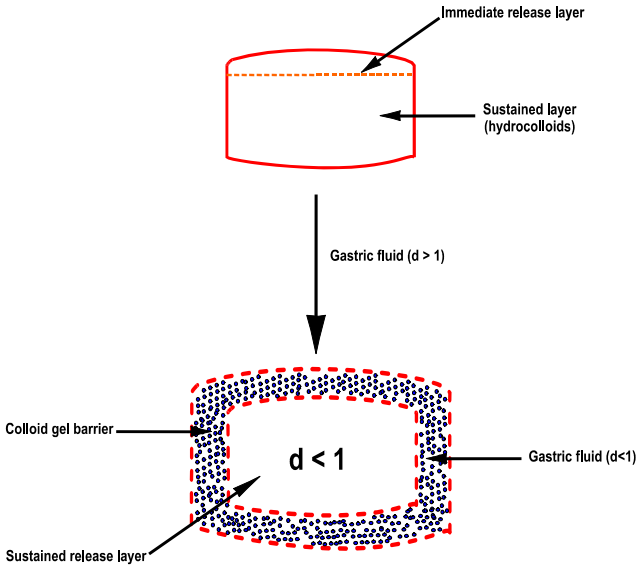

Fig. 5: Intra Gastric Bilayer Floating Tablet.

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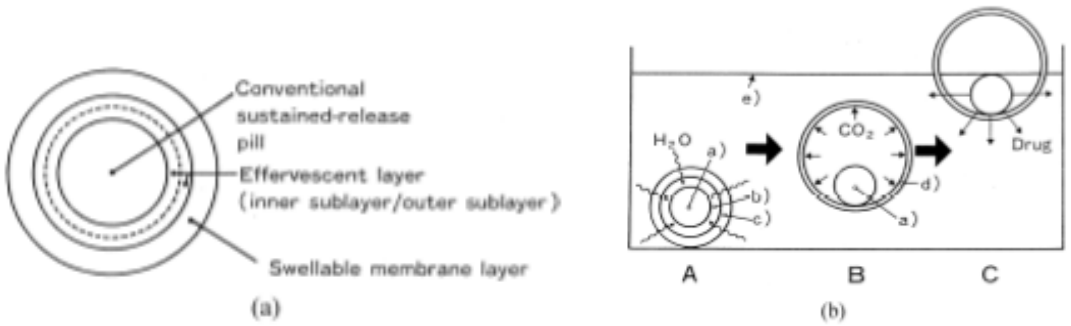

Fig. 6: (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

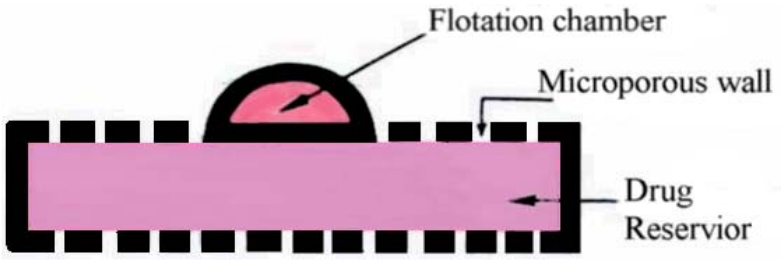

Fig. 7: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 9.

ISSN 2319-1082

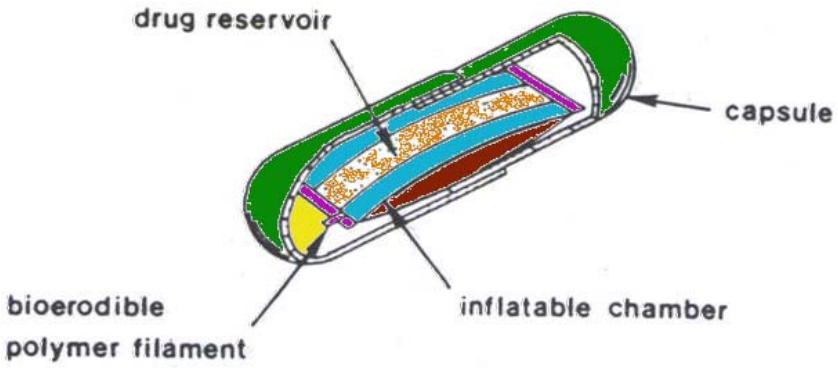

Fig. 8: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consist of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig. 10.

ISSN 2319-1082

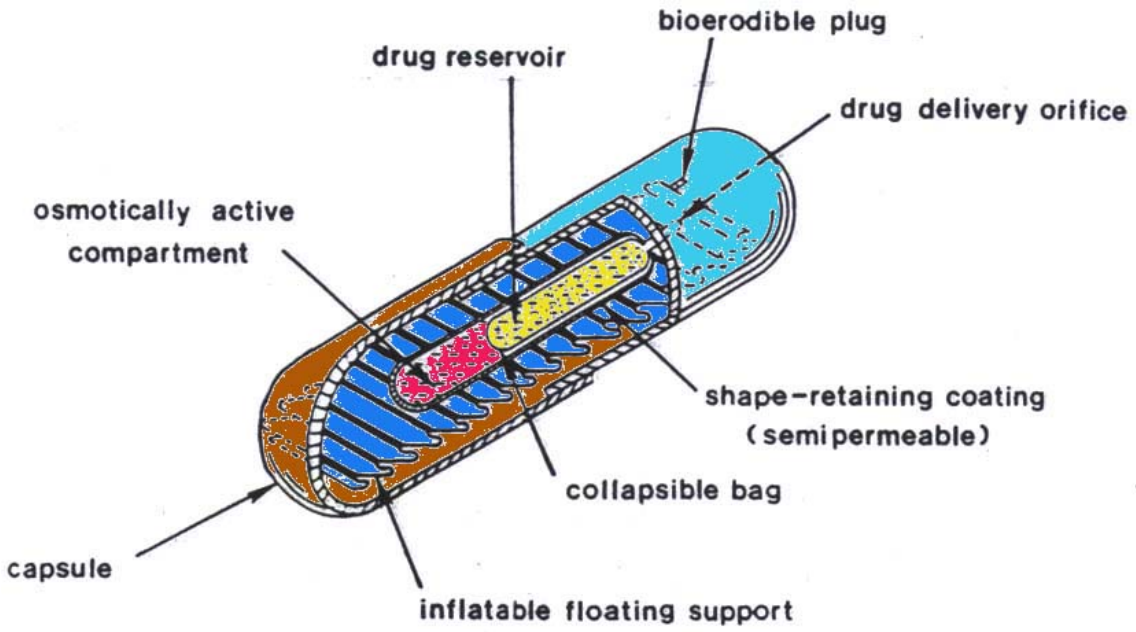

Fig. 9: Intragastric Osmotically Controlled Drug Delivery System

B. NON EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3. Alignate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation

ISSN 2319-1082

of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

Factors Controlling Gastric Retention Time of Dosage Form:[29]

The gastric retention time (GRT) of dosage form is controlled by several factors, that affect their efficacy as a gastroretentive system.

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.[30]
- Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.[31]
- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[32]
- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

ISSN 2319-1082

- Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- Gender – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- Age – Elderly people, especially those over 70, have a significantly longer GRT.
- Posture – GRT can vary between supine and upright ambulatory states of the patient.[33]
- Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.
- Biological factors – Diabetes and Crohn's disease.

CONCLUSION

For a prototype of oral drug delivery systems to be transformed into commercial dosage forms, a number of seemingly trivial, non-scientific questions need to be answered. This is something that scientists sometimes do not pay enough attention to. One good example is the polymeric excipients used in controlled drug delivery. Numerous new smart polymers have been created and used to develop environment-sensitive drug delivery systems, but none of them have been used in commercial formulations to date. One of the reasons for this general focus is that almost everybody is looking for polymers that are classified as generally regarded as safe (GRAS). If a polymer, regardless of its nature, is not on the GRAS list, it will most likely not be considered in the development of commercial dosage forms. This is not surprising considering that no one prefers the use of a new polymer for the first time. The pharmaceutical industry spends hundreds of millions of dollars in Phase I clinical testing of new drug compounds, and yet they are reluctant to spend a modest amount of money in testing the toxicity of new polymeric excipients. Over the last few years, the pharmaceutical industry has seen patent expiries for major blockbuster drugs which have resulted in losses worth billions. More blockbuster drugs are about to lose patent in the coming years. In such a situation, pharmaceutical companies are increasingly adopting various drug delivery systems to enhance their product efficacy, patient compliance and extend patent lives through innovative repositioning and reformulations of existing drugs. This has resulted in significant growth in the drug delivery market over the last few years. According to GBI Research, the overall drug delivery market is forecasted to grow to to $199 billion in 2016 from $101 billion in 2009, at a CAGR of 10.3%.Further advances in oral controlled-release dosage forms depend on uses of novel polymers, and it would be highly desirable if the pharmaceutical industry in general finds a mechanism to support such activity as testing new polymers and classifying them with GRAS status. Companies that focus on drug delivery technologies are usually small and may not be able to afford the high cost of toxicity testing of novel polymers. Support from larger companies is required more than ever. Developing oral drug delivery systems

ISSN 2319-1082

based on novel polymers will eventually help everyone involved in the pharmaceutical industry. The area of controlled drug delivery is an exciting and challenging area, and thanks to the many researchers involved and their collective concerted efforts, there is great promise and bright prospects for the future of healthcare.

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